

Hepatic Veno-Occlusive Disease following Stem Cell Transplantation: Incidence, Clinical Course, and Outcome

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The occurrence of hepatic veno-occlusive disease (VOD) has been reported in up to 60% of patients following stem cell transplantation (SCT), with incidence varying widely between studies depending on the type of transplant, conditioning regimen, and criteria used to make the diagnosis. Severe VOD is characterized by high mortality and progression to multiorgan failure (MOF); however, there is no consensus on how to evaluate severity. This review and analysis of published reports attempts to clarify these issues by calculating the overall mean incidence of VOD and mortality from severe VOD, examining the effect of changes in SCT practice on the incidence of VOD over time, and discussing the methods used to evaluate severity. Across 135 studies performed between 1979 and October 2007, the overall mean incidence of VOD was 13.7% (95% confidence interval [CI] = 13.3%-14.1%). The mean incidence of VOD was significantly lower between 1979-1994 than between 1994-2007 (11.5% [95% CI, 10.9%-12.1%] vs 14.6% [95% CI, 14.0%-15.2%]; $P < .05$). The mortality rate from severe VOD was 84.3% (95% CI, 79.6%-88.9%); most of these patients had MOF, which also was the most frequent cause of death. Thus, VOD is less common than early reports suggested, but the current incidence appears to be relatively stable despite recent advances in SCT, including the advent of reduced-intensity conditioning. The evolution of MOF in the setting of VOD after SCT can be considered a reliable indication of severity and a predictor of poor outcome.

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INTRODUCTION

Hepatic veno-occlusive disease (VOD) is a syndrome characterized by clinical features of rapid weight gain, ascites, painful hepatomegaly, and jaundice [1]. It is more common after allogeneic stem cell transplantation (SCT) than after autologous SCT,

with the most common precipitating event being the administration of conditioning therapy for hematopoietic SCT [1-3]. Historically, VOD has been reported in up to 60% of patients after SCT, ranging in severity from a mild, reversible disease to a severe syndrome associated with multiorgan failure (MOF) and death [1,4-7].

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VOD is thought to be caused by damage to sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus, the area surrounding the central veins. Sinusoidal obstruction is prominent, leading to proposals for an alternate or complementary terminology of sinusoidal obstruction syndrome (SOS) [4,8,9]. However this has not been universally adopted; thus the acronym “VOD (SOS)” is used to both reflect this debate and provide some consensus [10]. The pathogenesis is complex, involving cytokine release, endothelial injury, hemostatic activation, and hepatic drug detoxification through the glutathione pathway [3,11,12]. Hepatocellular necrosis, fibrosis, and vascular occlusion ultimately lead to liver failure, hepatorenal syndrome, MOF, and death.

The first case reports describing VOD as a direct complication of SCT appeared in 1979 [13,14]. Since then, numerous retrospective and prospective studies have been performed to determine the incidence of VOD, define risk factors, and assess the efficacy of prophylactic and treatment modalities. Two separate groups in the United States have proposed clinical criteria for the diagnosis of VOD in SCT recipients to preclude the need for histological confirmation of the disease (Table 1) [4,6].

In addition, prognostic classification (ie, mild, moderate, or severe) has been frequently quoted in the literature and in retrospective studies, primarily based on outcome [5]. As a tool for estimating prognosis, Cox regression analysis was used by Bearman et al. [7] to generate risk curves predictive of severe VOD derived from a large cohort of patients from the Seattle Transplant Registry. The investigators evaluated VOD occurring after the use of 1 of 3 specific chemotherapeutic regimens: cyclophosphamide and total body irradiation (TBI), busulphan and cyclophosphamide, or cyclophosphamide, BCNU, and VP-16. In this study severe VOD was associated with a case fatality rate of 98% by day +100 after SCT. Calculations based on total serum bilirubin and percentage weight gain at various time points subsequent to SCT, up to day +16 [7]. Similar models have not been proposed for other temporal or therapeutic settings, and models based on potential surrogates (eg, cytokines, endothelial stress products, markers of fibrosis) have yet to be fully defined [15]. Moreover, whereas there has been general agreement on the use of clinical criteria for diagnosing VOD, no definitive consensus has been reached on a suitable classification of severity of the disease, due to the limitations of existing methods [16-18].

This review analyzes data from the published literature, including a recent survey exploring the role of defibrotide in treating severe VOD/MOF as part of a randomized Phase II dose-finding trial [19,20]. The objectives were to (1) define the incidence of VOD after SCT and examine how this has changed over time

Table 1. Clinical Criteria for the Diagnosis of VOD

Original Seattle Criteria [4]	Baltimore Criteria [6]
Presence before day 30 post-SCT of 2 or more of the following: <ul style="list-style-type: none"> • Bilirubin ≥ 2 mg/dL (≈ 34 μmol/L) • Hepatomegaly, right upper quadrant pain • Ascites with or without unexplained weight gain of $>2\%$ over baseline 	Bilirubin ≥ 2 mg/dL before day 21 post-SCT and at least 2 of the following: <ul style="list-style-type: none"> • Hepatomegaly (usually painful) • Ascites • Weight gain $>5\%$ over baseline

The modified Seattle criteria [5] require presentation of the clinical features of VOD before day 20 post-SCT.

with increased sophistication of SCT procedures; (2) explain the wide variation in VOD incidence reported in the literature; (3) identify the most commonly used classifications for “severe” VOD and discuss the limitations of these methods; (4) identify factors with predictive value for the evolution of severe disease, such as the development of MOF; and (5) determine expected outcomes for patients with severe VOD or with VOD with MOF when only supportive care is available.

METHODS

Clinical literature was accessed through the PubMed database using the search terms “veno-occlusive disease” (and variations on this term), “incidence,” “stem cell transplantation” (and variations), “bone marrow transplantation (and variations), and “multiorgan failure” (and variations). Records from 1979 to October 2007 were included. A separate Medline search and bibliographies from articles obtained by both search methods also were examined for references not included in the database searches. A total of 387 citations were recovered; of these, 149 relevant articles (full tabular listing available from the corresponding author on request) were selected for detailed examination and analysis by 2 reviewers independently, using the inclusion and exclusion criteria outlined below. Where several articles reported on the same cohort of patients, the studies were considered as a single report to avoid duplication of data in the analysis (11 studies arranged into 4 groups). Of the final set of 142 studies, the incidence of VOD in the study group was reported in 135. The remaining 7 studies had missing or incomplete data for overall incidence of VOD but nonetheless were included in the review because they contained specific information on the incidence of and mortality from severe VOD.

Our analysis includes all retrospective data analyses, prospective cohort studies, and clinical trials addressing the incidence of VOD, as well as the degree of severity of VOD after SCT, published between 1979 and October 2007. For studies comparing parameters in subgroups of patients (eg, variations in conditioning regimens with standard conditioning),

the overall incidence of VOD is presented. For studies investigating VOD prophylaxis, incidence and outcome data from historical or contemporary controls only (when available) were considered; however, administration of heparin or ursodiol prophylaxis for VOD during SCT may not have been clearly documented if it was not relevant to the theme of the article. Data are conflicting on the efficacy of heparin or ursodiol prophylaxis in VOD; although authors have reported a possible beneficial effect [21-25], most studies (including the large multicenter European Group for Blood and Marrow Transplantation [EBMT] study of more than 1600 SCT recipients) have found neither form of prophylaxis to be effective in reducing the incidence of VOD [2,16,26-30]. Therefore, rather than exclude such studies from the analysis, the overall incidence of VOD was used, making it impossible to distinguish between patients receiving or not receiving prophylaxis with heparin or ursodiol.

Of the 347 citations recovered, 198 were excluded from the final analysis based on criteria applied in the following chronological sequence: *in vitro* or animal studies ($n = 1$), studies in languages other than English ($n = 30$; some of these were revised and published in English-language journals), review articles ($n = 41$), and studies including <50 subjects ($n = 93$). VOD is a rare disease with reported incidences as low as 0%; thus, studies including <50 SCT recipients were unlikely to yield statistically significant data on the incidence of and outcome from VOD. Studies in which prophylactic defibrotide was administered were excluded ($n = 8$). The remaining exclusions ($n = 25$) were a mixture of case reports, case-control studies, and other studies where the incidence of or outcome from VOD could not be determined from the text.

To validate this analysis of outcome from severe VOD reported in the literature, we also have presented historical control data from a recent survey conducted by our multicenter study group that explored the role of defibrotide for the treatment of severe VOD/MOF as part of a randomized Phase II dose-finding trial [19,20]. These data were not included in the main analysis, but serve to illustrate that severity criteria based on the evolution of MOF compare favorably with existing severity criteria and are predictive of VOD outcome. For this survey, retrospective data were collected at 3 of the participating centers (City of Hope National Medical Center, Memorial Sloan Kettering Cancer Center, and M.D. Anderson Cancer Center). Data were collected for 38 patients, all of whom had severe VOD as defined by the study criteria during the 5 years before Institutional Review Board approval of the study at each site. Eligible patients (adult and pediatric) met the Baltimore criteria (Table 1) by day +21 post-SCT and were diagnosed with encephalopathy and/or renal dysfunction and/or

pulmonary dysfunction by day +28. Exclusion criteria included preexisting cirrhosis, viral hepatitis, and graft-versus-host disease involving the liver or gut, clinically significant bleeding, inability to maintain blood pressure except with multiple vasopressors, and treatment with defibrotide. Complete response was defined by complete resolution of the signs and symptoms of VOD after provision of the best available care. Outcome data for survival at day +100 post-SCT were collected and reviewed centrally at the Dana-Farber Cancer Institute.

Statistical Methods

A comprehensive data analysis was performed using the following *a priori* techniques modeled on a meta-analytic approach. Elementary descriptive statistics for the overall incidence of VOD in the articles reviewed were expressed as frequency, percentage, mean (plus 95% confidence interval [CI]), minimum, maximum, and median values. The 95% CIs were calculated according to the method of Gardner and Altman [31]; for smaller samples, a more complex method for calculating 95% CIs described by Armitage and Berry [32], was used. These statistical parameters were calculated for the complete set of 135 articles reporting incidence data, as well on selected subsets of articles as defined by the selection criteria (eg, type of transplant, VOD criteria used for the diagnosis) (Table 2 and Figure 1). Where both the Baltimore and the Seattle criteria were applied to define the incidence of VOD in the same population of patients, only the incidence according to the more commonly used Seattle criteria was included in the statistical analysis. Survival data for the defibrotide study group were analyzed using χ^2 and Kaplan-Meier tests.

RESULTS

A total of 135 reports of VOD occurring in populations of >50 SCT patients were included in this analysis. (A full tabular listing is available in the supplement.) In these 135 studies, out of a total of 24,920 SCT recipients, 3425 developed VOD. The mean incidence of VOD was 13.7% (95% CI, 13.3%-14.1%), with absolute values ranging from 0 to 62.3% (Table 2 and Figure 1). However in the majority of studies (130/135), the variation in incidence was much smaller than this, ranging from 0 to 40%. Only 5 studies reported an incidence of VOD $>40\%$; all of these studies included high-risk patient groups [5,33-36].

There were marked differences among studies depending on the criteria used for diagnosis and the type of transplant performed (Table 2 and Figure 1). Using the Seattle criteria, the mean incidence of VOD was

Table 2. Descriptive Statistics for VOD Incidence from 135 Publications

Group	Number of Studies	Total Number of Patients	Number of Patients with VOD	Mean Incidence, %	95% CI	Min, %	Max, %	Median, %
1. All patients	135	24,920	3425	13.7%	13.3-14.1	0	62.3	13.3
2. Baltimore	33	5261	503	9.6%	8.8-10.4	0	28.9	8.6
3. Seattle	78	14,798	2565	17.3%	16.7-17.9	0	62.3	17.0
4. Auto-SCT	19	3967	344	8.7%*	7.8-9.4	1.5	44.1	6.2
5. Allo-SCT	67	11,285	1453	12.9%*	12.3-13.5	0	62.3	12.0
6. Pre-1994	50	10,943	1260	11.5†	10.9-12.1	1	62.3	9.3
7. Post-1994	74	12,234	1805	14.6†	14.0-15.2	0	53.3	15.4

* $P < .001$.† $P < .05$.

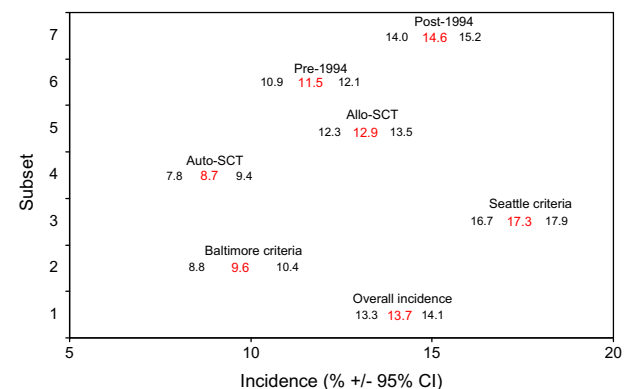
17.3% (95% CI, 16.7%-17.9%; range, 0-62.3%), whereas with the Baltimore criteria, the mean incidence was 9.6% (95% CI, 8.8%-10.4%; range, 0-28.9%), reflecting the increased stringency of the Baltimore criteria for diagnosing VOD. In 24 studies, the criteria used were not specified. The mean incidence of VOD was lower in studies that specifically reported data on autologous SCT recipients compared with those specifically reporting on allogeneic SCT (8.7% [95% CI, 7.8%-9.4%] vs 12.9% [95% CI, 12.3%-13.5%]; $P < .001$). The incidence range also was much narrower in studies reporting data on autologous SCT (0-12% in 13/18 studies vs 0-40% for allogeneic SCT in 53/57 studies). The 5 studies that reported an incidence exceeding 12% after autologous SCT were performed in high-risk patient groups [37-41].

A subanalysis of the data was undertaken to compare the mean incidence of VOD across studies reporting on patients undergoing transplantation before and after 1994, to assess the impact of high-resolution HLA matching and other technological advances since that time, such as the use of less hepatotoxic conditioning regimes [2,42]. Surprisingly, the incidence of VOD calculated across 50 out of 135 studies reporting on 10,943 patients who underwent SCT before 1994 was only 11.5% (95% CI, 10.9%-12.1%), compared with 14.6% (95% CI, 14.0%-15.2%) in 74 of 135 studies (12,234 patients) who underwent SCT after 1994 ($P \leq .05$). The timing of SCT was not clearly reported in the remaining 11/135 studies, and these were excluded from this calculation.

The incidence of severe VOD was specifically reported in 42 studies, in which it ranged from 0 to 77% of all cases of VOD. In 14 of these 42 studies, the method used to classify severity of VOD was not reported [24,43-55]. In studies that did specify which method was used, the most common classification (23/42 articles) was the retrospective system proposed by the Seattle group [2,5,16,22,34,36,39,40,56-70]. In this classification system, patients with mild disease demonstrate no apparent adverse effects of liver disease, require no medications for diuresis of excessive fluid or for hepatic pain, and have completely revers-

ible signs, symptoms, and laboratory abnormalities. Patients with moderate disease experience adverse effects from liver disease, require sodium restriction and diuretics to minimize signs of fluid excess (eg, edema) or medication to alleviate pain from hepatomegaly, and eventually demonstrate complete resolution of all signs of liver damage (ie, return of weight to baseline, decrease in liver size, and decrease in total serum bilirubin to $<34.2 \mu\text{mol/L}$ [2 mg/dL]). In severe VOD, patients demonstrate adverse effects from liver disease; signs, symptoms, and laboratory values do not resolve before day +100; or death occurs [5]. Only 2 of the 42 studies used the Bearman model alone [35,71], and another 2 studies used a combination of the Bearman model and retrospective Seattle classification [72,73]. Severe VOD also was classified based on the presence of MOF in combination with the Bearman criteria in studies by Wadleigh et al. [71] and Bajwa et al. [74], and based on MOF combined with the retrospective criteria in studies by Cesaro et al. [67], Sucak et al. [75], and Haussman et al. [76]. In these studies, MOF was defined as an oxygen requirement (oxygen saturation $\leq 90\%$ in room air and/or ventilator dependence) and/or renal dysfunction (defined as a doubling of baseline creatinine and/or dialysis dependence) and/or encephalopathy, in addition to liver failure [77].

The mortality rate in patients with severe VOD was specifically documented in 19 studies

**Figure 1.** Graphical representation of the data presented in Table 1.

[2,5,36,40,43,45,46,50,55,56,59,62,63,70,72,76,78-80]. The overall mortality from severe VOD across all 19 of these studies was 84.3% (198/235 patients; 95% CI, 79.6%-88.9%). Fifteen of the 19 studies reported a mortality rate exceeding 75% when only supportive treatment was available [2,5,36,40,45,50,55,59,62,63,70,72,76,78,80]. In 12 of the 19 studies, only limited information on the cause of death in patients with severe VOD was provided, but in the other 7, death from severe VOD was commonly associated with the development of MOF [5,40,45,50,56,76,78,80]. The correlation between severe VOD with MOF and high mortality was further validated by comparison with the defibrotide study group data [19,20]. This survey revealed a day +100 mortality of 79%, with 8 of 38 patients alive at this time point. Analysis by the χ^2 test demonstrated a strong statistical association between complete response and day +100 survival ($P < .0001$), with a kappa coefficient of 0.885 (95% CI, 0.808-0.962), as also reflected by a 88% day +100 mortality in the nonresponders (Table 3 and Figure 2).

DISCUSSION

An early prospective study to determine the incidence of VOD associated with SCT reviewed 255 consecutive patients undergoing bone marrow transplantation for malignancy between 1978 and 1980 [4]. Fifty-three patients (21%) met the Seattle criteria for the diagnosis of VOD (Table 1). The accuracy of these criteria was demonstrated by comparing this data with histological findings in a cohort of 64 patients who underwent biopsy or autopsy.

Jones et al. [6] retrospectively evaluated 235 consecutive patients who underwent bone marrow transplantation between 1982 and 1985. Histological diagnosis performed in a subsection of patients was found to correlate well with the presence of a consistent clinical syndrome of liver dysfunction occurring within the first 3 weeks after marrow infusion. The incidence of VOD using the Baltimore or Jones criteria was 22% (52/235), which was comparable with the Seattle series [4] (Table 1).

The conclusion from both the original Seattle and Baltimore series was that VOD has a specific clinical presentation, which enables diagnosis without the need for liver biopsy. Both criteria are commonly used in clinical practice, but the Seattle criteria are quoted more frequently in the literature for defining the incidence of VOD among SCT recipients.

The largest multicenter prospective study to address incidence of VOD among SCT recipients was published in 1998 by the EBMT [2]. In that study, 1652 consecutive BMT patients were evaluated over a 6-month period in 73 participating EBMT centers for the occurrence of VOD according to Baltimore

Table 3. Historical Patients with Severe VOD: CR and Mortality Correlation at Day +100 Post-SCT (n = 38)

	Number of Patients	Survived to Day +100
Patients with CR	4/38 (11%)	4/4 (100%)
Nonresponders	34/38 (89%)	4/34 (12%)

criteria. VOD was diagnosed in 87 patients overall (incidence, 5.3%; 95% CI, 4.2%-6.4%). There was a 3-fold difference in incidence between allograft and autograft recipients (8.9% and 3.1%; respectively; $P < .0001$), representing a significantly increased relative risk of VOD after allogeneic SCT compared with autologous SCT.

In some studies, both Baltimore and Seattle criteria were applied to the same cohort of patients, demonstrating significant differences in the incidence of VOD depending on the criteria used [30,65,72,81,82]. This may account for some of the observed variation in VOD incidence in other studies. By definition, all patients meeting the Baltimore criteria also satisfy the Seattle criteria, but not vice versa. The Baltimore criteria result in a lower rate of VOD diagnosis and less variation in the incidence of VOD among studies (Table 1). The increased stringency of the Baltimore criteria comes from the requirement for hyperbilirubinemia of >34 mmol/L, compared with >27 mmol/L in the Seattle criteria, and the need for the presence of 2 or more additional clinical features of VOD, compared with only one additional feature in the Seattle criteria (Table 2) [81]. Blostein et al. [81] applied both sets of criteria to a cohort of 101 SCT recipients and noted that a larger proportion of patients with VOD diagnosed by the Baltimore criteria died from severe disease at an early stage compared with those diagnosed by the Seattle criteria. They concluded that the Baltimore criteria identify more patients at increased risk of poor outcome.

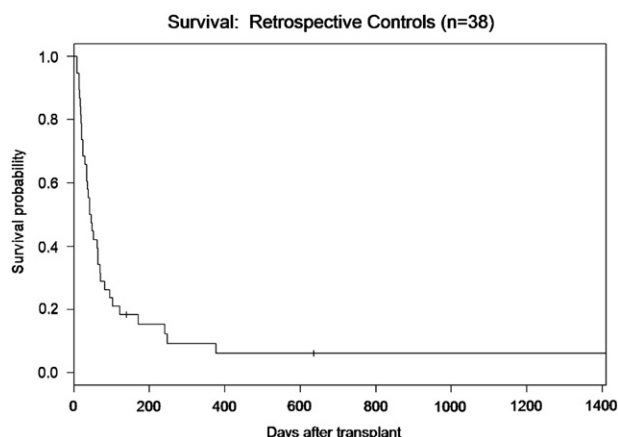


Figure 2. Kaplan-Meier survival curve for retrospective historical controls with severe VOD (MOF) (n = 38).

In addition to the diagnostic criteria used, other differences in study design, including endpoints and methods of data reporting, contribute to the between-study variation in VOD incidence. Many studies rely on retrospective data extraction, which is highly dependent on the accuracy and extent of documentation and, to a lesser extent, on the perceptions of the attending physician [83,84]. The development of jaundice after SCT often is attributable to multiple causes, including cholestasis, likely resulting in underdiagnosis or overdiagnosis of VOD in many cases [83,84]. Although clinical criteria appear to be adequate for a diagnosis of VOD in the majority of patients, recent interventional studies have sought to confirm the diagnosis by histological and other means in confounding cases [77,85,86].

In the second study published by the Seattle group in 1993 [5], VOD developed in 190 of 355 patients (incidence, 54%; 95% CI, 48%-59%). The clinical criteria used for that study were similar to those developed in the 1984 study [4], but with the stipulation that the clinical features of VOD appear within 20 days of transplantation (the modified Seattle criteria). Three additional studies from that group have reported similarly high occurrences of VOD [36,58,64]. The increased incidence noted in the more recent reports compared with the incidence of 21% in the 1984 Seattle study was attributed to increased use of intensive high-dose conditioning regimens.

Similarly, the lower incidence of VOD reported in the 1998 EBMT study was thought to be related to the variable frequency of risk factors, patient selection, definitions of VOD used by different centers, and advances in HLA typing of allogeneic grafts since the 1993 Seattle report [47]. This is illustrated by the fact that the majority of the patients in the Seattle series received an allogeneic transplant and high-dose chemotherapy, compared with only 29% of those in the EBMT study. Indeed, when patients with several risk factors for VOD in the EBMT study were analyzed separately, the incidence was similar to that reported in the Seattle series. Other factors that likely contributed to the lower incidence of VOD reported in the EBMT and other studies include the widespread use of BEAM (BCNU, etoposide, cytarabine, and melphalan) conditioning (a regimen that lacks major sinusoidal liver toxins) for autologous SCT in Europe, and the historical administration of lower doses of TBI in European centers compared with their US counterparts [87].

In some of the smaller and more recent series reviewed here, no VOD was reported in the study population [88-90]. This may be due to both small sample size and improved understanding of the biology of SCT, allowing modification of transplantation protocols to minimize toxicity. For example, lower incidences of VOD and other transplantation-related

complications have been reported with the use of reduced-intensity conditioning (RIC) protocols [88,91], i.v. or targeted busulfan (dose-adjusted according to individual patient pharmacokinetics) [72,92-94], T cell depletion [62,65,88,89,92,95], and fractionation of the TBI dose used for SCT conditioning [96-100]. It is known that fewer SCT complications arise when HLA-matched siblings are used as donors [98,101-103], and in the last decade, the advent of high-resolution HLA typing has led to a significantly reduced complication rate and improved outcome for SCT patients overall [104].

Despite these advances, our current analysis suggests that the overall incidence of VOD has actually increased over time. The reason for this is unclear, but in some studies specific strategies, such as i.v. dosing of busulfan in children, have been associated with more VOD rather than less, suggesting that such measures are not uniformly protective in all SCT populations [105]. Other contributing factors have included extension of the age limit for transplantation by more widespread use of RIC protocols, the use of multiple alkylating regimens in certain pediatric populations (eg, neuroblastoma), reservation of SCT for patients with relapsed or resistant disease due to advances in novel remission induction therapy, introduction of promising but potentially toxic new agents for graft-versus-host disease prophylaxis (eg, sirolimus, everolimus), second or third SCT in patients encountering secondary malignancies after cure of their first, and the increasing use of mismatched donors [37,38,104,106-109].

The variation in the reported incidence of VOD is multifactorial, reflecting differences among studies in the type of transplant, conditioning regimen, other drugs received, primary disease, coexisting medical conditions, risk factors for liver toxicity, study design, and the criteria used to make the diagnosis [15,81,110]. Thus, a limitation of our analysis is that the data were not stratified according to such variables. Conversely, the strength of the study is the large number of patients included, which made it possible to obtain useful information about the overall incidence of VOD among SCT recipients.

Although the Seattle and Baltimore criteria have become widely accepted as standards for clinical diagnosis, there has been less agreement among researchers on a suitable classification for the severity of VOD [2,16,17]. The classification based on the retrospective assessment of outcome for the cohort of 355 patients in the 1993 Seattle study identified 54 patients with severe VOD. Although death was not the only requirement for assignment to the severe VOD category in this study, 53/54 patients (98%) died by day +100.

This retrospective classification system was used in the 1998 EBMT study [2]. The incidence of severe VOD in those patients was 27.6% (24/87), which is comparable with the incidence in the Seattle cohort

[5]. The mortality from all causes in this group of patients with severe VOD was 100%. Importantly, a similar incidence of severe VOD by this definition after allogeneic and autologous SCT has been reported in several smaller studies [16,22,39,46,58,63,65], but a much higher incidence of severe VOD (around 50%) has been reported in allograft recipients [36,47,49,50,57,62,111]. The large EBMT study reported a 3-fold higher incidence of VOD in allogeneic SCT recipients (8.9% vs 3.1%; $P < .0001$), but did not include a separate analysis of the incidence of and mortality from “severe” disease (defined retrospectively) between autologous and allogeneic SCT patients. Given that allogeneic SCT is associated with greater immunologic and cytokine-mediated disturbances, the incidence of severe VOD and death would be expected to be higher in allogeneic SCT recipients, an observation also supported by more recent studies [77].

A prospective risk-benefit analysis is needed before any interventional trial using agents with potentially harmful side effects to treat VOD, such as recombinant tissue plasminogen activator (rtPA) [73,112]. For this purpose, data from the second Seattle cohort of 355 patients were used to develop a logistic regression model [7]. This model was found to have a specificity exceeding 90%, and its accuracy was tested on a cohort of similarly conditioned patients at the same center. However this model was specifically developed to justify a clinical trial of rtPA in VOD, which has the potential for serious hemorrhagic complications. It applies only to those patients receiving certain specific regimens of intensive cytoreductive therapy for hematologic malignancy [113] and accounts for only the first 16 days post-SCT, which is before VOD develops in a significant proportion of patients [40,57,114]. Despite these limitations, investigators have found this model to be useful, particularly when the proposed treatment is associated with serious side effects [73].

Because of the limitations of existing criteria for evaluating the severity of VOD, the evolution of MOF in patients with VOD has been suggested as a more reliable indicator of both severity and outcome [17,67,71,74-77,113,115,116]. Importantly, the relationship between severe VOD and MOF was analyzed in the Seattle cohort study using time-dependent proportional hazards models. MOF was common in patients with severe VOD compared with patients with mild or moderate VOD ($P < .001$) [5]. Similarly, Jones et al. [6] reported that many patients with VOD died with MOF in the Baltimore cohort of 235 SCT patients. More recently, in a cohort study of 199 SCT patients, Haire and coworkers [117-120] found that the occurrence of VOD was often predictive of the subsequent development of MOF and increased mortality. A series of other reports have demonstrated that the development of MOF in patients after SCT is associated with high mortality (60%-100%) regardless of

the etiology [121-127]. More specifically, hepatic dysfunction after SCT is often predictive of later MOF [117-120,128] and greatly reduces the likelihood of surviving MOF [129]. For instance, elevated bilirubin is a known risk factor for the development of acute renal failure (ARF) [130-132]. ARF after SCT rarely occurs in isolation and usually occurs as part of MOF including the liver, often manifested as VOD [40,50,61,128,133]. This association between severe VOD and ARF has been reported in numerous studies [5,16,39,62,114,125,133-136], and the combination of VOD with ARF and/or mechanical ventilation as a result of pulmonary dysfunction is associated with especially high mortality, particularly in the pediatric population [125,126,131,135,137-139].

The Seattle study found that mortality from severe VOD commonly resulted from progressive MOF and rarely from liver failure *per se* [5,140]. Thus, the investigators concluded that all transplantation-related causes of death should be considered in the assessment of outcome in such patients. In support of this, 16/24 patients with severe VOD in the EBMT series died from VOD (corresponding to 1% of the whole series, 18.4% of VOD patients, and 66.7% of those with severe VOD) [2]. However, the remaining 8 patients with severe VOD in that report died before day +100 from a related cause, including sepsis. Thus, the all-cause mortality at day +100 was 100%. Jones et al. [6] also reported high mortality from MOF with VOD (47%; 24/52) in the Baltimore cohort. Several other studies also have reported MOF as the major cause of death in patients with severe VOD [21,74,141]. Consequently, VOD with MOF has been used to prospectively define severe VOD in current clinical studies of therapy for VOD, such as rtPA and defibrotide [74-77,113,115,116], and the evolution of MOF in patients with VOD has become widely accepted as an indication of severity and a predictor of poor outcome [17,67,71,74,76,77,113,115,116].

It is noteworthy that the exploratory historical controls in the survey performed by the defibrotide study group demonstrate a mortality rate of 79% at day +100, which is similar to the 84.3% mortality estimated from the other studies reviewed here. Notable exceptions in the literature analysis included a multicenter study based in Philadelphia that reported a mortality of only 30% in patients with severe VOD [5,56], and a study by Vassal et al. [46] in which the method for determining severity was not defined. These outliers highlight an additional problem with interpreting the retrospective severity criteria: what constitutes “resolution of the symptoms and signs of liver disease by day +100”? Minor elevations in bilirubin or serum transaminase concentration are common after SCT and are often due to the effects of drugs, such as cyclosporin. A recent publication reported a correlation between increasing serum bilirubin value in VOD

patients with time and mortality, and noted that the increase in mortality for a given increase in bilirubin value is greater when the starting value was lower [142]. This suggests that patients with a high bilirubin level at presentation that remains stable are less likely to die than patients with a low bilirubin level that rises rapidly. Therefore, the retrospective evaluation of severity of VOD can be subjective, may result in erroneous classification, and has poor predictive value for outcome. We propose that classification of VOD severity should include concurrent organ dysfunction in at least one other system (eg, renal failure) to fulfill a requirement for MOF, and as such should be universally accepted by the transplantation community as the definitive replacement for previous classification systems.

In summary, despite recent advances, such as molecular HLA typing and the use of less-toxic SCT protocols, a small but significant increase in the mean incidence of VOD over time is reported in the published literature. The overall incidence of VOD is much lower than was indicated in early reports. However, the combination of clinical criteria with diagnostic tests, facilitated by advances in our understanding of the histopathology underlying VOD, should lead to increased diagnostic accuracy in confounding cases and thus reduce variation between future studies.

Severe VOD is associated with a mortality rate >80% on day +100 post-SCT based on our analysis, and is most frequently associated with hepatorenal syndrome and progression to MOF. The evolution of MOF in patients with VOD has become widely accepted as a reliable and clinically useful indicator of severity and outcome of VOD, and our analysis supports this view.

Future research directions will include large surveys of current SCT databases for incidence and outcome. Given that more innovative approaches to treatment of this disease are required, prospective studies of promising therapeutic and prophylactic interventions should be used as a platform to validate clinical features, prediction of outcome, and surrogate markers of severe VOD.

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